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1*H*-Indazole and 2*H*-indazole derivatives of androsta-5,16-dien-3β-ol

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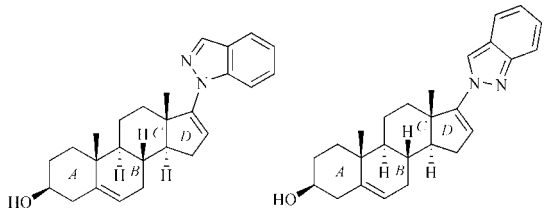
The title compounds, 17-(1*H*-indazol-1-yl)androsta-5,16-dien-3β-ol, (I), and 17-(2*H*-indazol-2-yl)androsta-5,16-dien-3β-ol, (II), both $C_{26}H_{32}N_2O$, have an indazole substituent at the C17 position. The six-membered *B* ring of each compound assumes a half-chair conformation. A twist of the steroid skeleton is observed and reproduced in quantum-mechanical *ab initio* calculations of the isolated molecule using a molecular orbital Hartree–Fock method. In the 1*H*-indazole derivative, (I), the molecules are joined in a head-to-head fashion *via* O—H···O hydrogen bonds, forming chains along the *a* axis. In the 2*H*-indazole derivative, (II), the molecules are joined in a head-to-tail fashion with one of the N atoms of the indazole ring system acting as the acceptor. The hydrogen-bond pattern consists of zigzag chains running along the *b* axis. Substituted steroids have proven to be effective in inhibiting androgen biosynthesis through coordination of the Fe atoms of some enzymes, and this study shows that indazole-substituted steroids adopt twisted conformations that restrict their intermolecular interactions.

Comment

Androgen biosynthesis is mediated by steroidal 17α-hydroxylase-$C_{17,20}$-lyase (CYP17), which catalyzes the conversion of C_{21} precursors (pregnenolone and progesterone) to the related C_{19} steroids (dehydroepiandrosterone and androstenedione) in the testis and the adrenals (Nakajin, Hall & Onoda, 1981; Nakajin, Shively *et al.*, 1981; Nakajin & Hall, 1981; Zuber *et al.*, 1986; Hall, 1991). Effective inhibitors of these enzymes could be useful in the treatment of androgen-dependent diseases, such as prostate cancer. A number of steroidal and nonsteroidal compounds which inhibit CYP17 have been reported (Barrie & Jarman, 1996; Jarman *et al.*, 1998; Njar & Brodie, 1999; Hartmann *et al.*, 2002; Leroux, 2005; Hakki & Bernhardt, 2006; Moreira *et al.*, 2008). Amongst them, an interesting class of steroidal inhibitors has been reported in which the azole group is attached at position C17 of the steroid nucleus through an N atom (Njar *et al.*, 1996, 1998; Handratta *et al.*, 2005). Inhibitors of this class have shown potent inhibition of CYP17 as well as other important biological activities (Njar *et al.*, 1998; Handratta *et al.*, 2005). Attempts have been made to correlate the structure of the molecule with its lesser or greater ability to coordinate to the Fe atom of the haem group of the enzyme, thus inhibiting its function (Cavalli & Recanatini, 2002; Schappach & Holtje, 2001).



We report here the molecular structures of (I) and (II) determined by single-crystal X-ray analysis, and compare them with those of the free molecules, as given by quantum-mechanical *ab initio* calculations, and with 17-(3-pyridyl)-androsta-5,16-dien-3β-ol, a related compound with potent CYP17 inhibition properties.

Molecular views of (I) and (II) are shown in Figs. 1 and 2. In both compounds, the *A*/*B* junction is quasi-*trans* and the remaining rings are *trans*-fused. The hydroxy substituents at C3 are positioned in the β face of the *A* rings, with angles to the Cremer & Pople (Cremer & Pople, 1975) normal of ring *A* of 70.30 (16) and 71.43 (11)°, respectively, for (I) and (II). Ring *A* exhibits the usual slightly flattened chair conformation, with average torsion angles of 51.77 (15) and 51.89 (11)°

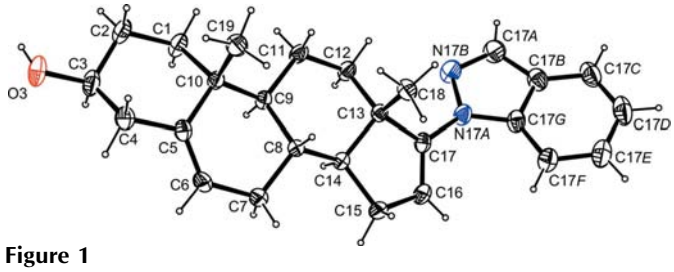


Figure 1
A view of the molecule of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented as small spheres of arbitrary radii.

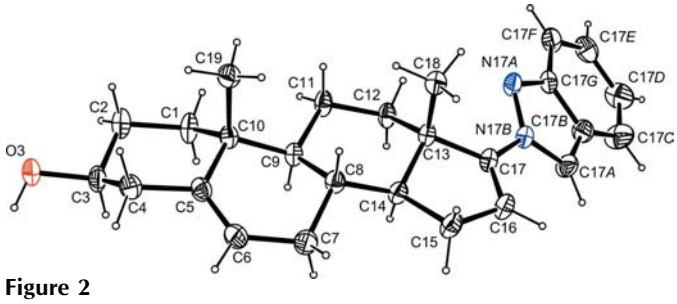


Figure 2
A view of the molecule of compound (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are represented as small spheres of arbitrary radii.

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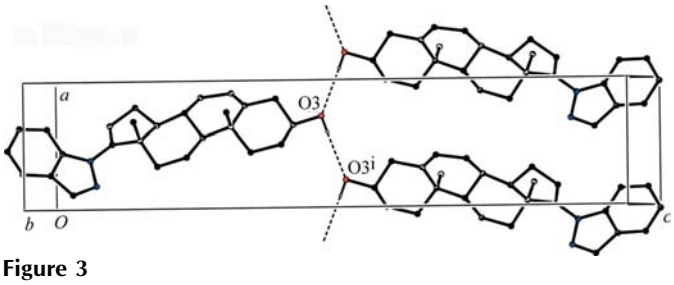

Figure 3
A partial packing view, showing the formation of chains in (I) through O—H···O hydrogen bonds (dashed lines). H atoms not involved in hydrogen bonds have been omitted for clarity. [Symmetry code: (i) $x-\frac{1}{2}$, $\frac{3}{2}-y$, $1-z$.]

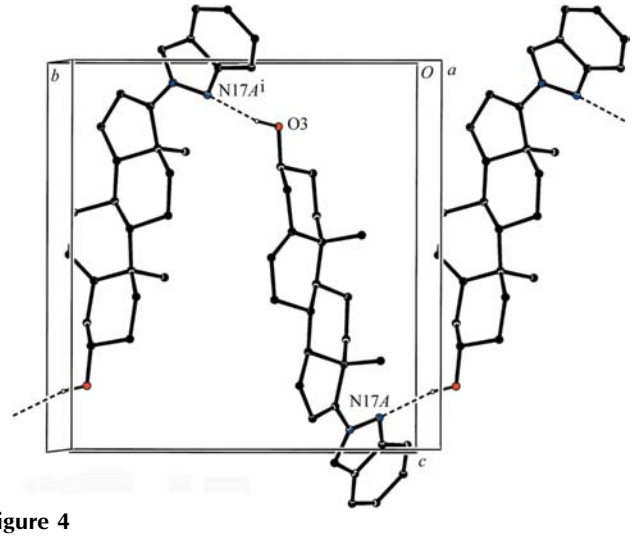

Figure 4
A partial packing view, showing the formation of zigzag chains in (II) through O—H···N hydrogen bonds (dashed lines). H atoms not involved in hydrogen bonds have been omitted for clarity. [Symmetry code: (i) $1-x$, $\frac{1}{2}+y$, $1-z$.]

for (I) and (II), respectively. Ring *B*, with two pairs of electrons shared between atoms C5 and C6, conforms to a half-chair shape, with average torsion angles of 35.6 (1) and 37.97 (10)° for (I) and (II), respectively. More specifically, the puckering parameters (Cremer & Pople, 1975) for these rings are given in Table 3. They are roughly identical for both compounds, confirming the chair conformation for ring *A* and a conformation similar to a half-chair for ring *B*. Ring *C* exhibits the usual slightly flattened chair conformation, with average torsion angles of 56.1 (1) and 54.80 (8)° for (I) and (II), respectively. Ring *D*, with a C16═C17 double bond, shows a conformation that can be described as envelope on C14, with P = 16.3 (3) and τ = 34.5 (2)° [P = 8.9 (2) and τ = 36.7 (2)° for (II)]. The substituents at C17 are in equatorial positions; the C17—N17*A* bond makes an angle of 87.8 (2)° to the normal of the Cremer & Pople plane in (I), and the C17—N17*B* bond makes an angle of 78.31 (15)° in (II). The pseudo-torsion angle C19—C10···C13—C18 that measures the twist of the steroid skeleton is 9.5 (5)° for (I) and 10.9 (5)° for (II). The distances between terminal atoms C3 and C17 are 8.684 (5) and 8.661 (5) Å for (I) and (II), respectively.

In order to check whether the large twist of the molecules is intrinsic to the free steroid molecule or due to intermolecular interactions, we performed quantum-mechanical calculations of the equilibrium geometry of the free molecule. These calculations were performed using the computer program *GAMESS* (Schmidt *et al.*, 1993). A molecular-orbital Roothan Hartree–Fock method was used with an extended 6-31G(d,p) basis set. Tight conditions for convergence of both the self-consistent field cycles and the maximum density and energy gradients were imposed (10^{-5} atomic units). The calculations reproduce the twist (calculated pseudo-torsion angle of 10° and calculated C3···C17 distance of 8.7 Å for both compounds). Overall, there is good agreement between the calculated and experimental parameters; the bond lengths do not differ by more than 0.02 Å and the bond angles differ by a maximum of 3°. There is also good agreement in the orientation of the substituent indazole ring systems, showing the small freedom of rotation of the indazole group around the C17—N bond. For (I), the experimental torsion angle N17*B*—N17*A*—C17—C13 is −43.7 (4)° and the calculated value is −43.7°. For (II), the N17*A*—N17*B*—C17—C13 torsion angle is 14.3 (3)° and the calculated value is 14.4°.

There is a strong hydrogen-bond donor at the head of both compounds and possible acceptors in the tail but the hydrogen-bond networks are very different. In (I), there is a chain formation, with hydrogen bonds of the O—H···O type joining the molecules head-to-head. The chains run along the *a* axis with a short periodicity of three elements (Table 1 and Fig. 3). In (II), the molecules are joined head-to-tail, with atom N1 of the indazole ring system acting as an acceptor. Zigzag chains with a periodicity of 14 elements can be seen running along the *b* axis (Table 2 and Fig. 4). In 17-(3-pyridyl)androsta-5,16-dien-3β-ol, the molecules are joined head-to-tail, the twist of the steroid skeleton is only 5.91°, the steroid length is 8.895 Å and the angle between the least-squares plane of ring *D* and of the C17 substituent ring is 30.58 (15)° (Burke *et al.*, 1995).

Experimental

Both compounds were synthesized according to the method reported previously by Moreira *et al.* (2007). Compound (I) was crystallized from acetone by slow evaporation. Compound (II) was crystallized from a mixture of acetonitrile and THF (2:1 *v*/*v*) by slow evaporation.

Compound (I)

Crystal data

$C_{26}H_{32}N_2O$
M_r = 388.54
Orthorhombic, $P2_12_12_1$
a = 6.04450 (10) Å
b = 12.1149 (2) Å
c = 28.9321 (4) Å
V = 2118.66 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.07 mm^{-1}
T = 293 (2) K
0.22 × 0.15 × 0.03 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
T_{min} = 0.915, T_{max} = 0.998
48693 measured reflections
2520 independent reflections
1985 reflections with $I > 2\sigma(I)$
R_{int} = 0.057

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3A···O3^{i}	0.80 (6)	2.45 (5)	3.233 (4)	167 (6)

Symmetry code: (i) $x-\frac{1}{2}, -y+\frac{3}{2}, -z+1$.

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
O3—H3···N17A^{i}	0.85 (5)	2.09 (5)	2.924 (3)	167 (4)

Symmetry code: (i) $-x+1, y+\frac{1}{2}, -z+1$.

Table 3
Comparison of the puckering parameters for compounds (I) and (II).

Ring	Q (Å)	Q_2 (Å)	θ (°)	φ (°)	φ_2 (°)
(I)					
A	0.536 (3)		7.0 (3)	85 (3)	
B	0.491 (3)		50.7 (4)	214.2 (4)	
C	0.584 (3)		13.5 (3)	266 (1)	
D		0.345 (3)			214.0 (5)
(II)					
A	0.540 (2)		7.6 (2)	96 (2)	
B	0.496 (2)		50.8 (2)	212.4 (3)	
C	0.574 (2)		12.4 (2)	262 (1)	
D		0.367 (2)			208.0 (4)

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.040$
$wR(F^2) = 0.139$
$S = 1.09$
2520 reflections
267 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.23$ e Å^{-3}

Compound (II)

Crystal data

$C_{26}H_{32}N_2O$
$M_r = 388.54$
Monoclinic, $P2_1$
$a = 5.9234$ (2) Å
$b = 13.0938$ (4) Å
$c = 13.6623$ (4) Å
$\beta = 91.5347$ (16)°
$V = 1059.27$ (6) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.07$ mm^{-1}
$T = 293$ (2) K
0.37 × 0.20 × 0.09 mm

Data collection

Bruker APEX CCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2000)
$T_{min} = 0.884$, $T_{max} = 0.993$
36122 measured reflections
2855 independent reflections
2446 reflections with $I > 2\sigma(I)$
$R_{int} = 0.032$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.038$
$wR(F^2) = 0.120$
$S = 1.07$
2855 reflections
267 parameters
1 restraint
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}

O-bound H atoms were located in a difference Fourier map and their positional parameters were refined, with U_{iso}(H) = 1.5U_{eq}(O). All C-bound H atoms were refined as riding on their parent atoms, with C—H = 0.93–0.98 Å and U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(methyl C). The absolute configuration was not determined from the X-ray data but was known from the synthesis route. Friedel pairs were merged before refinement.

For both compounds, data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *ORTEPIII* (Burnett & Johnson, 1996), *ORTEP-3 for Windows* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3083). Services for accessing these data are described at the back of the journal.

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